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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,360	05/09/2005	Masanori Nakasu	P27827	4868

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/534,360	NAKASU ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,11 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,11 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. In Applicant's Response to the Non-Final Rejection, filed 7/10/2006, claims 6, 7, 9, 10, and 12-15 have been canceled, claims 1-3, 5, 8, 11, and 16 have been amended, and claims 17 and 18 are new claims. Claims 1-5, 8, 11, and 16-18 are under consideration.

Priority

2. Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Although priority papers have been submitted in the instant case, a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Objections

2. Claims 2 and 16 are objected to because of the following informalities: The amended claims recites "a porous block body" and "interconnecting holes communicate to each other". This recitation of "interconnecting holes communicate to each other" does not further specify any properties of "a porous block body". Therefore, the recitation of "interconnecting holes communicate to each other" is considered to be redundant and should be removed. Appropriate correction is required.

Claim 18 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claims 1 and 16 both require the use of a plasmid, pCAH.BMP2 (figure 1).

Claims 1 and 16 are objected to because of the following: The claims recite, "a recombinant plasmid as shown in Figure 1". The claims must be complete in themselves (see MPEP § 2173.05s) and therefore the instant incorporation by reference encompassed by "as shown in Figure 1" would not be considered a complete disclose. Applicant should provide structural language to disclose the intended recombinant plasmid. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

3. Claims 1-, 8, 11, and 16, rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, have been adequately amended to enable the instant invention, and therefore this rejection is withdrawn.

Applicant traverses this rejection that the present amendment is responsive to each point raised by the Office Action. Upon consideration of the amended claims,

Applicant's arguments have been found persuasive, and therefore, the rejection is withdrawn.

Biological Deposit

4. Claims 1-5, 8, 11, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ biological matter, specifically a recombinant plasmid as shown in figure 1, which discloses pCAH.BMP2. Since the biological materials are essential to the claimed invention, they must be obtained by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C.§ 112 may be satisfied by a deposit of the biological materials. The specification does not disclose a repeatable process to obtain the biological materials and it is not apparent if the biological materials are readily available to the public. It is noted that Applicant has deposited the biological materials, but there is no indication in the specification of public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over her or her signature and registration number, stating that the specific biological have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent,

would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over her or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained I a public depository for a period of 30 years or 5 years after the last request or the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R.§ 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention id directed to M.P.E.P §2411.05, as well as to 37 C.F.R.§ 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information. Finally, Applicant is advised that the address for the

ATCC has recently been changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection

10801 University Boulevard

Manassas, VA 20110-2209

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-16, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, have been amended to clarify the claims. Therefore the rejection is withdrawn.

Claim 1 and 16 specifically recited "a base sequence derived from an expression plasmid". The metes and bound of a "base sequence" were deemed as being unclear.

Applicant traversed these arguments on the grounds that this recitation would be clear to an artisan. This argument was not found persuasive. However, Applicant removed this recitation and specified a nucleic acid encoding a BMP-2. This amendment clarified the issue. Therefore, the rejection is withdrawn.

6. Claims 1-16, rejected under 35 U.S.C. 112, second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, have been amended to clarify the claims. Therefore the rejection is withdrawn.

Claims 1 and 16 were rejected for the recitation of "derived". The metes and bounds of "derived" are also considered vague and indefinite because it can have a broad range of interpretations.

Applicant did not address this rejection in their remarks section. However, the term, "derived", was removed in the amendment. Therefore, its rejection is moot and therefore withdrawn.

7. Claims 1-16, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, have been amended to clarify the claims. Therefore this rejection is withdrawn.

Claims 1 and 16 specifically recited " a non-viral vector holding the nucleic acid". The metes and bound of this phrase were deemed to be unclear.

Applicant traversed these arguments on the grounds that this recitation would be clear to an artisan. This argument was not found persuasive. However, applicant removed this language and replaced it with "a cationic liposome for adsorbing the recombinant plasmid". This amendment clarified the issue. Therefore, the rejection is withdrawn.

8. Newly added claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims recites, "using the recombinant plasmid as a template". The metes and bounds of this recitation are vague and indefinite. It is unclear what is meant by "using' or how the recombinant plasmid is to be used. It is also unclear how or for what the recombinant plasmid is to serve as a template.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-8 and 11-16, rejected under 35 U.S.C. 103(a) as being unpatentable over JP2001-505097 (translation of record), JP2000-302567 (translation of record) and Street et al. (PNAS 99(15):9656-9661, July 2002), have been amended and has overcome the art rejection. Therefore, the rejection is withdrawn.

Applicant traversed this rejection on the grounds that the art does not specifically teach a specific vector encoding BMP and that it does not teach a cationic liposome. The argument that the art does not teach a specific vector encoding BMP is not found persuasive because first the claims do not recite a specific vector and second because it still would have been obvious from Streets disclose to use BMP-2 in a gene therapy.

The instant claims are drawn to "a recombinant plasmid as shown in Figure 1". Given the broadest reasonable interpretation of "as shown in Figure 1", this recitation could be interpreted as a suggestion or example of what the recombinant plasmid can encompass. Therefore, while it may be the intent of Applicant to limit the specific vector of Figure 1, the claims still encompasses many other possible plasmid vectors.

As taught in the Non-Final Rejection, mailed 2/10/2006, Street teaches, "They also teach that angiogenic factors bFGF and BMP family involvement in bone repair and promote blood vessel formation. bFGF promotes osteoblast proliferation and augment fracture healing." Therefore an artisan would be motivated to use these factors in a gene therapy product for bone formation, as claimed, because they promote bone repair, blood vessel formation, osteoblast proliferation, and augment fracture healing.

However, the argument that the art does not specifically teach a cationic liposome was found persuasive. Therefore, the instant rejection is withdrawn.

10. Claims 1-8 and 11-16, rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat Ap 2002/0082694 A1, JP2000-302567 (translation of record) and Street et al. (PNAS 99(15):9656-9661, July 2002), have been amended and has overcome the art rejection. Therefore, the rejection is withdrawn.

This rejection was traversed same grounds as described in the rejection of above in 9 and the rejection withdrawn for the same reasons as described in 9.

11. Claims 1-5, 8, 11, and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP2001-505097 (translation of record), JP2000-302567 (translation of record), Flick (US Pat No. 6,096,303, pd-8/2/2000), and Street et al. (PNAS 99(15):9656-9661, July 2002).

The amended claims drawn to an osteogenic treatment device, comprising a recombinant plasmid encoding BMP-2; bFGF; a cationic liposome that carries the BMP-2 plasmid; and a porous block body comprising hydroxyapatite or tricalcium phosphate; wherein the bFGF is mixed with the BMP-2 plasmid, in which the mixing ratio between the bFGF and BMP-2 plasmid is in the range of about 10:1 to 1:100 by weight, and wherein in a case where the are (average) of the holes is defined as A and the maximum cross-sectional area (average) of the holes is defined as B, the value of B/A is in the range of 2 to 150.

JP2001-505097 teaches an osteogenic treatment device comprising a DNA encoding a protein of osteogenesis, more specifically a BMP family member and a

biodegradable porous matrix containing tricalcium phosphate ceramics with continuous micropores in the volume range of 20-60%. It also teaches a mixtures with other proteins for osteogenesis (p. 4 lines 13-18). It also teaches any suitable expression vector (p. 4 line 32). It does not teach specifically an angiogenic factor and the specific dimensions and properties of the instant invention.

JP2000-302567 teaches a sintered compact that is made of porous calcium phosphate with a porosity of 55 to 90% with spherical pores that communicate with one another. The average diameter of the communicating parts between the pored is not less than 50 .m and the pores diameters are not less than 150 .m. It also teaches the use for bone implants or replacements structures. JP2000-302567 does not teach the use with gene therapy.

Flick teaches a gene therapy method can utilize a cationic liposome to deliver a plasmid vector. Flick teaches that one would motivated to use a cationic liposome to deliver a vector because their use is well known in the art and readily adaptable for use in gene mediated therapies (par bridging col 6 and 7). Flick also further teaches that other carriers can be incorporated in mediating the gene therapy and delivery. Flick more specifically teaches the use of hydroxyapatite and teaches that it is useful in inducing or enhancing growth and proliferation of cells forming bone, especially osteoblasts (col 14, lines 38-41).

Street et al teach that the angiogenic factor are also osteogenic factors and therefore the two processes of angiogenesis in bone formation and generation of bone itself are inextricably linked. They teach that angiogenic factors bFGF and BMP family

involvement in bone repair and promote blood vessel formation. bFGF promotes osteoblast proliferation and augment fracture healing. These finding suggest that BMP family of gene could serve both the osteogenic and angiogenic limitations of the instant invention. Street et al also provides motivation for the use of VEGF in a therapy as being its involvement in coupling angiogenesis with bone formation and remodeling (p. 9661 Line bridging col 1 and 2). Street et al does not teach specific use in a device for osteogenic treatment nor does it teach a biocompatible body base with a the specific defining characteristics.

The embodiments of the ratio of protein mixture and a biocompatible base body would be obvious to one of ordinary skill in the art preparing device. An artisan would know that these parameters are dependent on the materials being use to produce the base body and also the BMP construct and the level of expression it provides as well as the properties of angiogenic factor being used in the mixture.

At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the knowledge and methods of JP2001-505097, JP2000-302567 (translation of record), Flick, provide a hydoxyapeptide porous block body that incorporated a BMP plasmid vector carried in a cationic liposome and bFGF as taught by Street et al. Street et al also provides motivation provide the motivations for the to consider the use of BMP and bFGF for it multipotent abilities in angiogenesis and osteogenesis. Flick provides motivation to use a cationic liposome for its well known use for gene delivery and easy of adaptability and hydroxyapatite for its ability to promote bone growth. Furthermore, it also would have been obvious to an artisan of

ordinary skill to use BMP vector and bFGF in a hydoxyapeptide porous block body with a reasonable expectation of success because they all have been used effectively in bone repair treatments.

12. Claims 1-5, 8, 11, and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat Ap 2002/0082694 A1, JP2000-302567 (translation of record), Flick (US Pat No. 6,096,303, pd-8/2/2000), and Street et al. (PNAS 99(15):9656-9661, July 2002).

The amended claims drawn to an osteogenic treatment device, comprising a recombinant plasmid encoding BMP-2; bFGF; a cationic liposome that carries the BMP-2 plasmid; and a porous block body comprising hydroxyapatite or tricalcium phosphate; wherein the bFGF is mixed with the BMP-2 plasmid, in which the mixing ratio between the bFGF and BMP-2 plasmid is in the range of about 10:1 to 1:100 by weight, and wherein in a case where the are (average) of the holes is defined as A and the maximum cross-sectional area (average) of the holes is defined as B, the value of B/A is in the range of 2 to 150.

US Pat Ap 2002/0082694 A1 teaches an osteogenic treatment device comprising a DNA encoding a protein of osteogenesis, more specifically a BMP family member and a biodegradable porous matrix containing tricalcium phosphate ceramics or hydroxiapetite dispersed into a collagen slurry as described in the instant specification [0021], [0025], [0007] & [0020]. It also teaches a mixtures with other proteins that are osteogenic enhancing factors [0028]. It does not teach specifically an angiogenic factor and the specific dimensions and properties of the instant invention.

JP2000-302567 teaches a sintered compact that is made of porous calcium phosphate with a porosity of 55 to 90% with spherical pores that communicate with one another. The average diameter of the communicating parts between the pored is not less than 50 .m and the pores diameters are not less than 150 .m. It also teaches the use for bone implants or replacements structures. JP2000-302567 does not teach the use with gene therapy.

Flick teaches a gene therapy method can utilize a cationic liposome to deliver a plasmid vector. Flick teaches that one would motivated to use a cationic liposome to deliver a vector because their use is well known in the art and readily adaptable for use in gene mediated therapies (par bridging col 6 and 7). Flick also further teaches that other carriers can be incorporated in mediating the gene therapy and delivery. Flick more specifically teaches the use of hydroxyapatite and teaches that it is useful in inducing or enhancing growth and proliferation of cells forming bone, especially osteoblasts (col 14, lines 38-41).

Street et al teach that the angiogenic factor are also osteogenic factors and therefore the two processes of angiogenesis in bone formation and generation of bone itself are inextricably linked. They teach that angiogenic factors bFGF and BMP family involvement in bone repair and promote blood vessel formation. bFGF promotes osteoblast proliferation and augment fracture healing. These finding suggest that BMP family of gene could serve both the osteogenic and angiogenic limitations of the instant invention. Street et al also provides motivation for the use of VEGF in a therapy as being its involvement in coupling angiogenesis with bone formation and remodeling (p.

9661 Line bridging col 1 and 2). Street et al does not teach specific use in a device for osteogenic treatment nor does it teach a biocompatible body base with a the specific defining characteristics.

The embodiments of the ratio of protein mixture and a biocompatible base body would be obvious to one of ordinary skill in the art preparing device. An artisan would know that these parameters are dependent on the materials being use to produce the base body and also the BMP construct and the level of expression it provides as well as the properties of angiogenic factor being used in the mixture.

At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the knowledge and methods of US Pat Ap 2002/0082694 A1, JP2000-302567 (translation of record) Flick, provide a hydoxyapeptide porous block body that incorporated a BMP plasmid vector carried in a cationic liposome and bFGF as taught by Street et al. Street et al also provides motivation provide the motivations for the to consider the use of BMP and bFGF for it multipotent abilities in angiogenesis and osteogenesis. Flick provides motivation to use a cationic liposome for its well known use for gene delivery and easy of adaptability and hydroxyapatite for its ability to promote bone growth. Furthermore, it also would have been obvious to an artisan of ordinary skill to use BMP vector and bFGF in a hydoxyapeptide porous block body with a reasonable expectation of success because they all have been used effectively in bone repair treatments.

13. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble

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